INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB2004/005421

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C405/00 C07C59/90 A61K31/5575 A61K31/192 A61P37/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, BEILSTEIN Data, WPI Data, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SZCZEPAN JOZEFOWSKI ET AL.: "Exogenous but not endogenous prostanoids regulate cytokine secretion from murine bone marrow dendritic cells: EP2, DP, and IP but not EP1, EP3, and FP prostanoid receptors are involved" INTERNATIONAL IMMUNOPHARMACOLOGY, vol. 3, 1 June 2003 (2003-06-01), pages 865-878, XP002325093 abstract paragraph '03.3! ----- -/--	11,15

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 April 2005	02/05/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Goetz, G

Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB2004/005421

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	NIALS A T ET AL: "AH13205, A SELECTIVE PROSTANOID EP2-RECEPTOR AGONIST" CARDIOVASCULAR DRUG REVIEWS, NEVA PRESS, BRANFORD, CT, US, vol. 11, no. 2, 1993, pages 165-179, XP009004866 ISSN: 0897-5957 the whole document	11,13, 15,17
P,X	VANCHERI C ET AL: "The lung as a privileged site for the beneficial actions of PGE2" TRENDS IN IMMUNOLOGY, ELSEVIER, CAMBRIDGE, GB, vol. 25, no. 1, January 2004 (2004-01), pages 40-46, XP004481206 ISSN: 1471-4906 the whole document	11,13, 15,17
X,P	KANDA N ET AL: "Prostaglandin E2 suppresses CCL27 production through EP2 and EP3 receptors in human keratinocytes" JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY, MOSBY - YEARLY BOOK, INC, US, vol. 114, no. 6, December 2004 (2004-12), pages 1403-1409, XP004666387 ISSN: 0091-6749 the whole document	12,16
A	HILLOCK C J ET AL: "INHIBITORY PROSTANOID EP RECEPTORS IN HUMAN NON-PREGNANT MYOMETRIUM" EUROPEAN JOURNAL OF PHARMACOLOGY, AMSTERDAM, NL, vol. 378, no. 1, 28 July 1999 (1999-07-28), pages 99-108, XP001124311 ISSN: 0014-2999 cited in the application the whole document	1
A	WO 03/037433 A (ALLERGAN, INC) 8 May 2003 (2003-05-08) cited in the application the whole document	1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB2004/005421

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 9, 10, 15 - 18 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

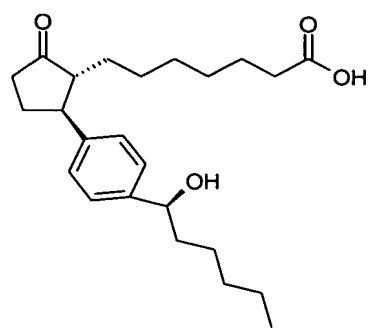
Information on patent family members

International Application No
PCT/GB2004/005421

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 03037433 A	08-05-2003	WO 03037433 A1	08-05-2003
		AU 2001297521 A1	12-05-2003
		CA 2426785 A1	08-05-2003
		EP 1438104 A1	21-07-2004

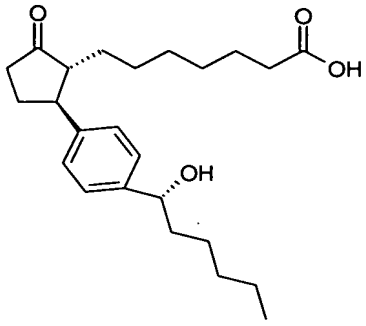
ABSTRACT

A compound selected from one of the following:



(1R,2S)-2-[4-(1-(S)-hydroxyhexyl)phenyl]-5-oxo-cyclopentaneheptanoic acid [RSS]

; or



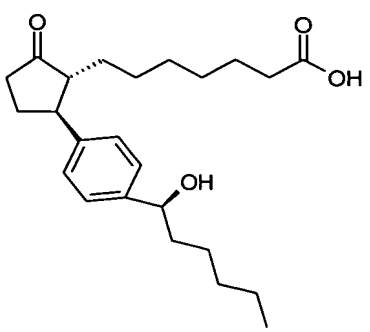
(1R,2S)-2-[4-(1-(R)-hydroxyhexyl)phenyl]-5-oxo-cyclopentaneheptanoic acid [RSR]

,

or a salt, solvate, chemically protected form or prodrug thereof, and its use in treating conditions alleviated by agonism of an EP_2 receptor.

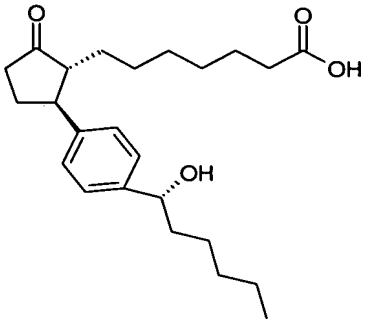
ABSTRACT

A compound selected from one of the following:



(1R,2S)-2-[4-(1-(S)-hydroxyhexyl)phenyl]-5-oxo-cyclopentaneheptanoic acid [RSS]

; or



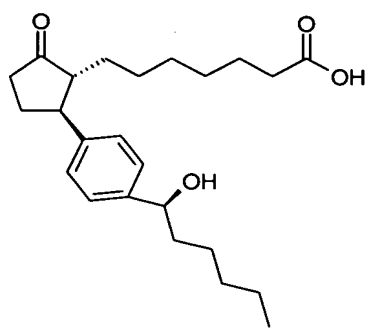
(1R,2S)-2-[4-(1-(R)-hydroxyhexyl)phenyl]-5-oxo-cyclopentaneheptanoic acid [RSR]

,

or a salt, solvate, chemically protected form or prodrug thereof, and its use in treating conditions alleviated by agonism of an EP_2 receptor.

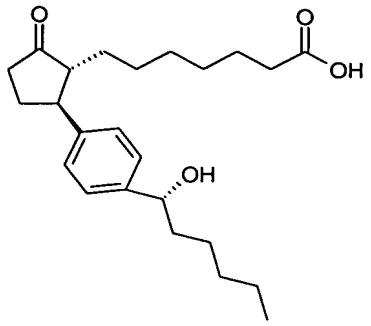
CLAIMS

1. A compound selected from one of the following:



(1R,2S)-2-[4-(1-(S)-hydroxyhexyl)phenyl]-5-oxo-cyclopentaneheptanoic acid [RSS]

; or

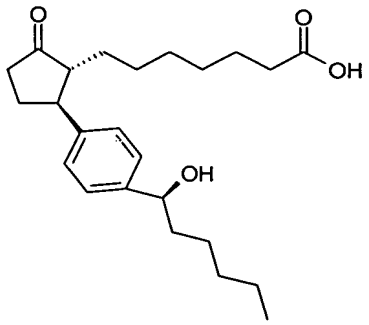


(1R,2S)-2-[4-(1-(R)-hydroxyhexyl)phenyl]-5-oxo-cyclopentaneheptanoic acid [RSR]

,

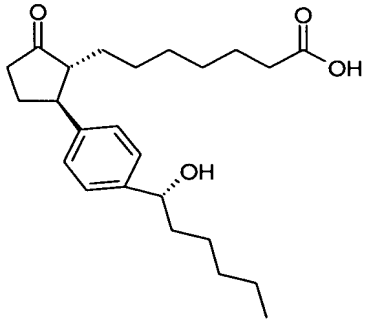
or a salt, solvate, chemically protected form or prodrug thereof.

2. (*trans*-2-[4-(1-hydroxyhexyl)phenyl]-5-oxo-cyclopentaneheptanoic acid, of which at least 90% by weight is selected from one of the following forms:



(1R,2S)-2-[4-(1-(S)-hydroxyhexyl)phenyl]-5-oxo-cyclopentaneheptanoic acid [RSS]

; or



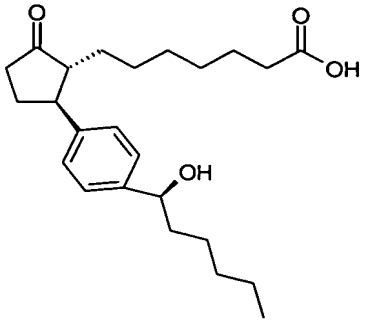
(1R,2S)-2-[4-(1-(R)-hydroxyhexyl)phenyl]-5-oxo-cyclopentaneheptanoic acid [RSR]

,

or a salt, solvate, chemically protected form or prodrug thereof.

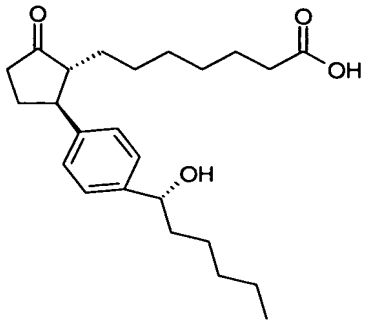
3. 2-[4-(1-hydroxyhexyl)phenyl]-5-oxo-cyclopentaneheptanoic acid, of which at least 80% by weight

is in one of the following forms:



(1R,2S)-2-[4-(1-(S)-hydroxyhexyl)phenyl]-5-oxo-cyclopentaneheptanoic acid [RSS]

; or



(1R,2S)-2-[4-(1-(R)-hydroxyhexyl)phenyl]-5-oxo-cyclopentaneheptanoic acid [RSR]

,

or a salt, solvate, chemically protected form or prodrug thereof.

4. A method of making a compound according to any one of claims 1 to 3.

5. A compound according to any one of claims 1 to 3, or a pharmaceutically acceptable salt thereof, for use in a method of therapy.

6. A pharmaceutical composition comprising a compound according to any one of claims 1 to 3, or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier or diluent.

7. The use of a compound according to any one of claims 1 to 3, or a pharmaceutically acceptable salt thereof in the preparation of a medicament for the treatment of a condition alleviated by agonism of an EP_2 receptor.

8. The use according to claim 7, wherein the condition alleviated by agonism of an EP_2 receptor is selected from the group consisting of: glaucoma, dysmenorrhoea and pre-term labour.

9. A method of treating a condition which can be alleviated by agonism of an EP_2 receptor, which method comprises administering to a patient in need of treatment an effective amount of a compound according to any one of claims 1 to 3, or a pharmaceutically acceptable salt thereof.

10. The method according to claim 9, wherein the condition alleviated by agonism of an EP_2 receptor is selected from the group consisting of: glaucoma, dysmenorrhoea and pre-term labour.

11. The use of an EP_2 receptor agonist, or a pharmaceutically acceptable salt thereof in the preparation of a medicament for the treatment of a condition alleviated by the inhibition of:

(i) human T-cell activation (proliferation);

(ii) the release of IL-2;

(iii) the release of TNF_α; or

(iv) the release of IFNγ.

12. The use of an EP_2 receptor agonist, or a pharmaceutically acceptable salt thereof in the preparation of a medicament for the treatment of psoriasis.

13. The use of an EP_2 receptor agonist, or a pharmaceutically acceptable salt thereof in the preparation of a medicament for the treatment of inflammatory lung diseases.

14. A use according to any one of claims 11 to 13, wherein the EP_2 receptor agonist is a compound of any one of claims 1 to 3.

15. A method of treating a condition which can be alleviated by the inhibtion of:

(i) human T-cell activation (proliferation);

(ii) the release of IL-2;

(iii) the release of TNF_α; or

(iv) the release of IFNγ;

which method comprises administering to a patient in need of treatment an effective amount of an EP_2 receptor agonist, or a pharmaceutically acceptable salt thereof.

16. A method of treating a psoriasis, which method comprises administering to a patient in need of treatment an effective amount of an EP_2 receptor agonist, or a pharmaceutically acceptable salt thereof.

17. A method of treating an inflammatory lung disease, which method comprises administering to a patient in need of treatment an effective amount of an EP_2 receptor agonist, or a pharmaceutically acceptable salt thereof.

18. A method according to any one of claims 15 to 17, wherein the EP_2 receptor agonist is a compound of any one of claims 1 to 3.

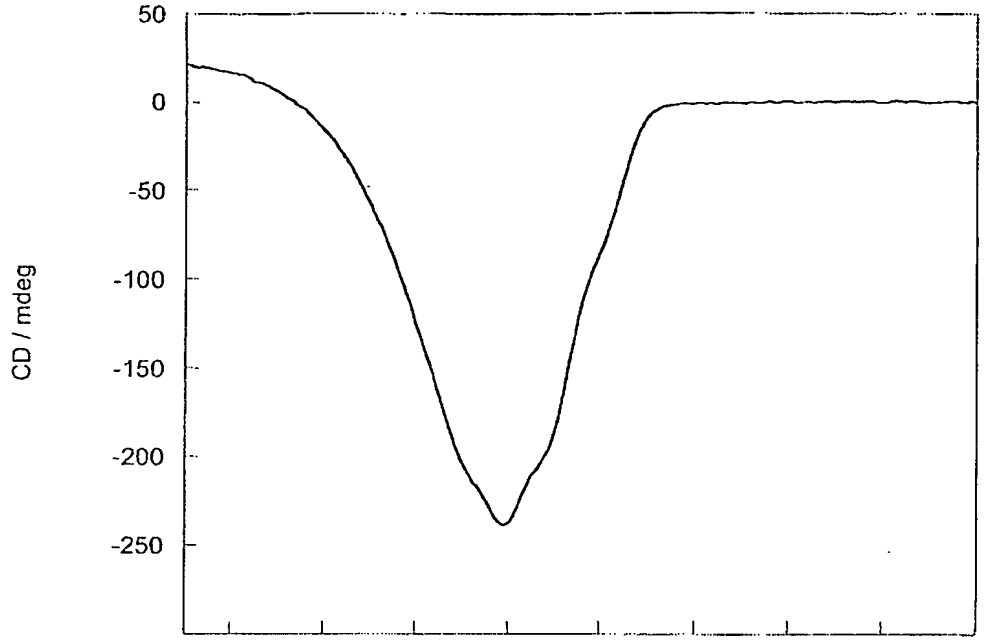

50
0
-50
-100
-150
-200
-250
CD / mdeg

Fig. 1a

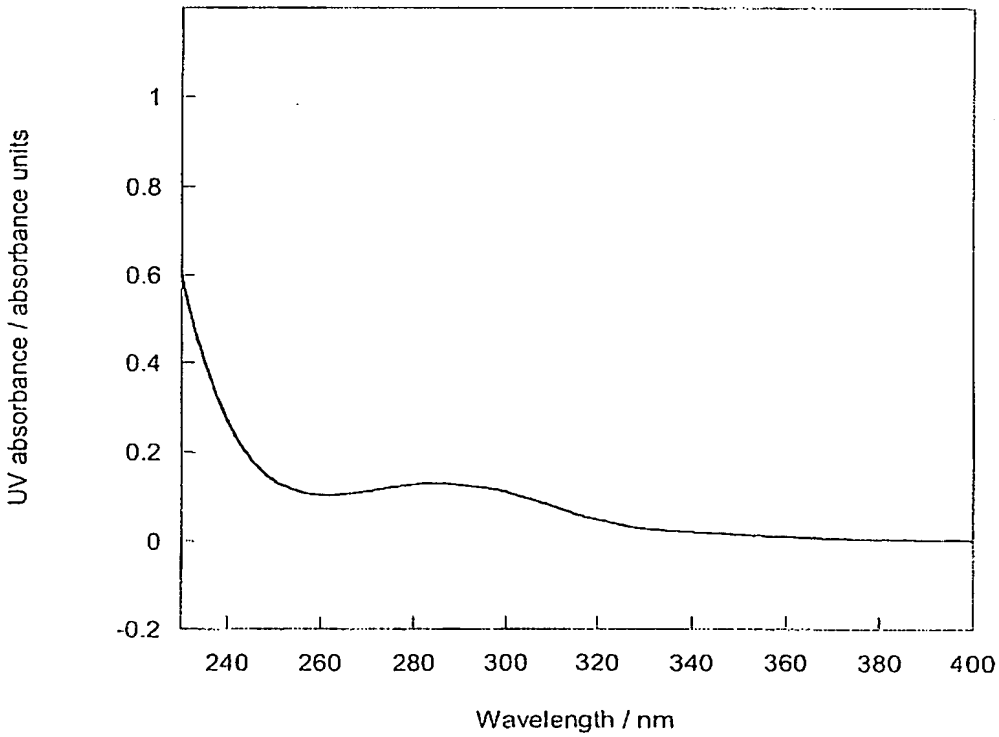

1
0.8
0.6
0.4
0.2
0
-0.2
240
260
280
300
320
340
360
380
400
UV absorbance / absorbance units
Wavelength / nm

Fig. 1b.

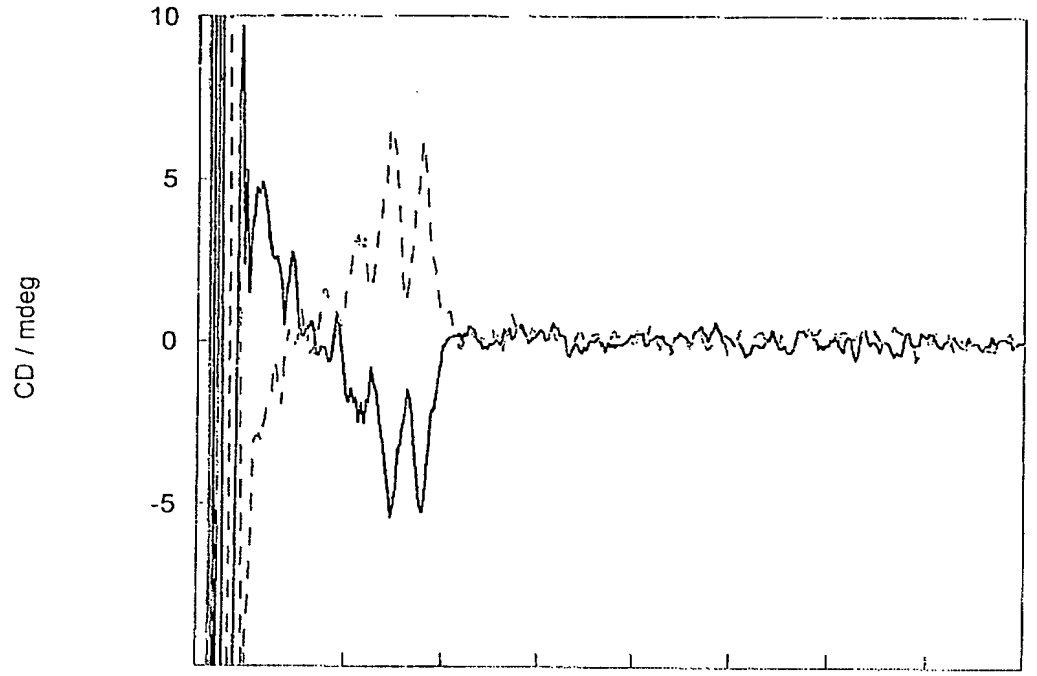

10
5
0
-5
CD / mdeg

Fig. 2a

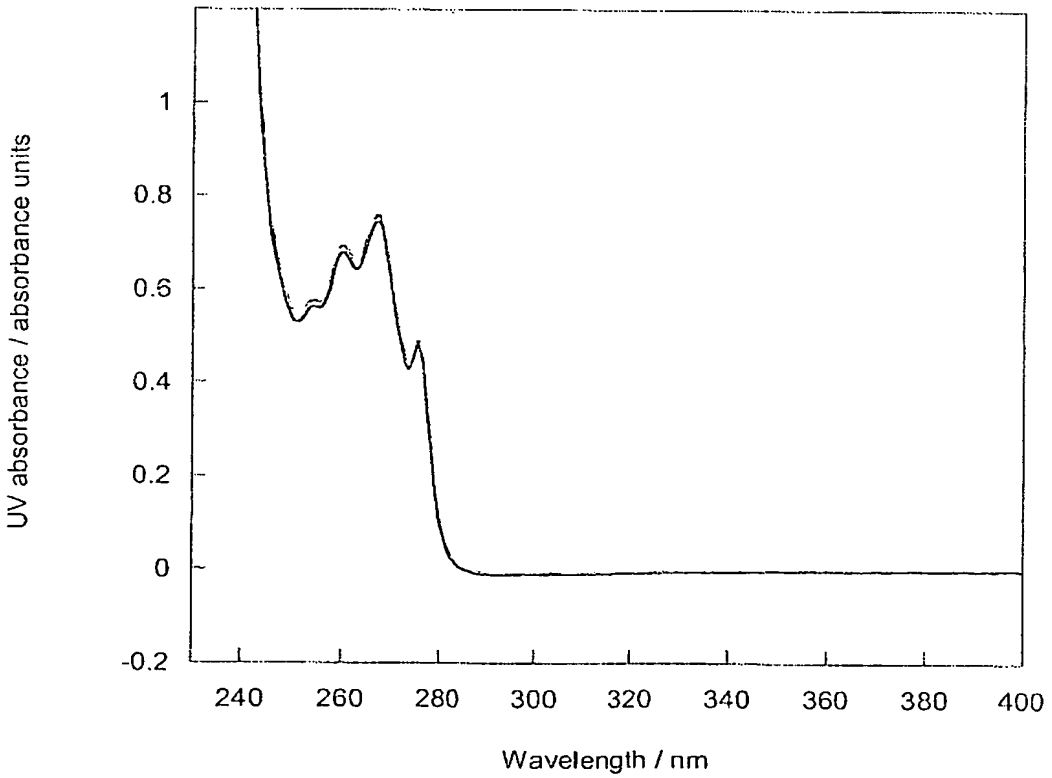

1
0.8
0.6
0.4
0.2
0
-0.2
UV absorbance / absorbance units
240
260
280
300
320
340
360
380
400
Wavelength / nm

Fig. 2b

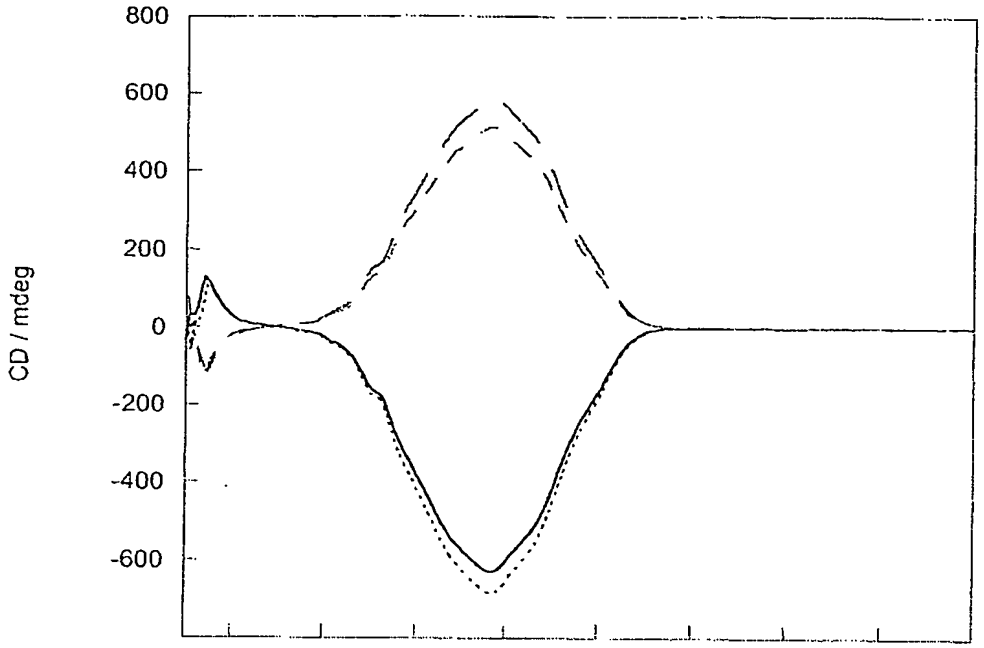

800
600
400
200
0
-200
-400
-600
CD / mdeg

Fig. 3a

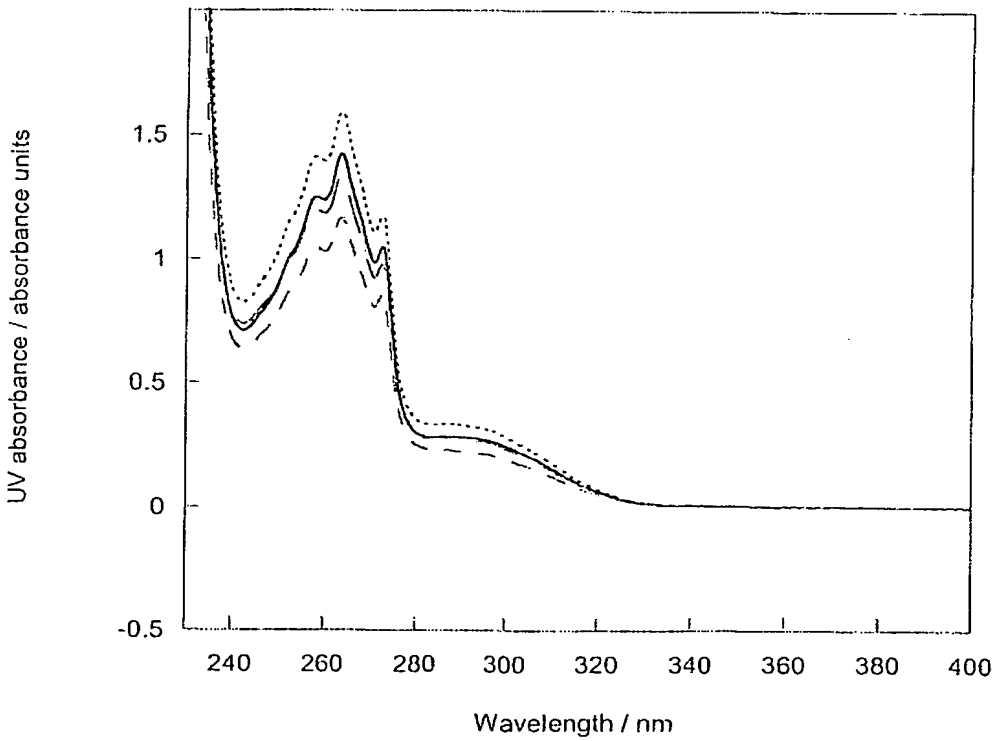

1.5
1
0.5
0
-0.5
240
260
280
300
320
340
360
380
400
UV absorbance / absorbance units
Wavelength / nm

Fig. 3b

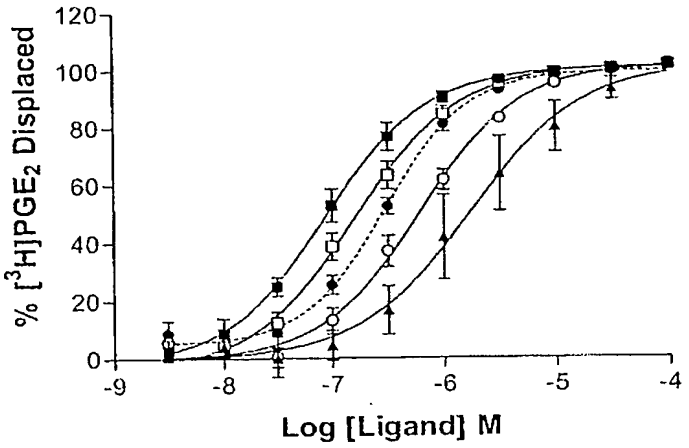

% [3H]PGE2 Displaced
120
100
80
60
40
20
0
-9
-8
-7
-6
-5
-4
Log [Ligand] M

Fig. 4

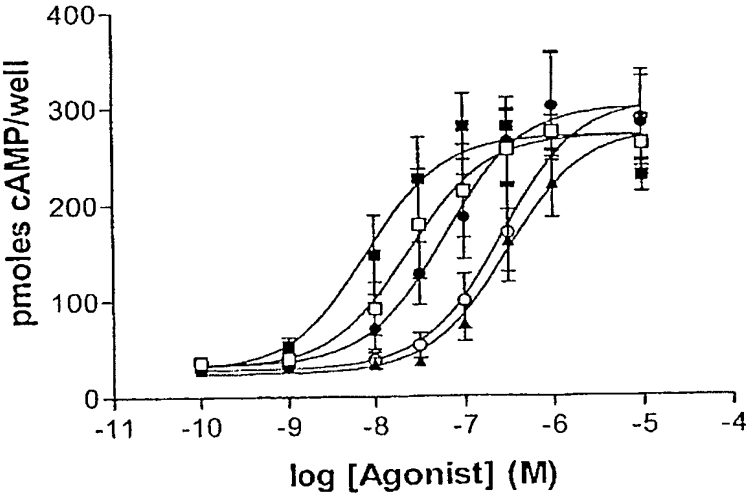

pmoles cAMP/well
400
300
200
100
0
-11
-10
-9
-8
-7
-6
-5
-4
log [Agonist] (M)

Fig. 5

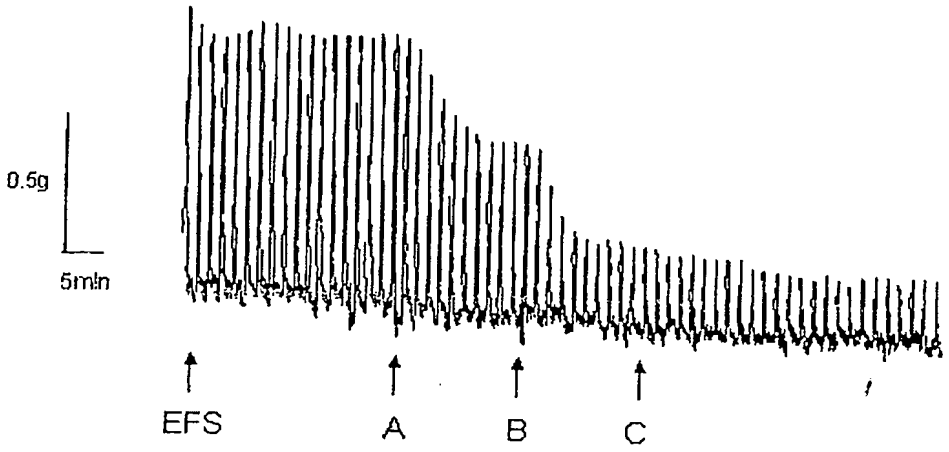

0.5g
5min
EFS
A
B
C

Fig. 6

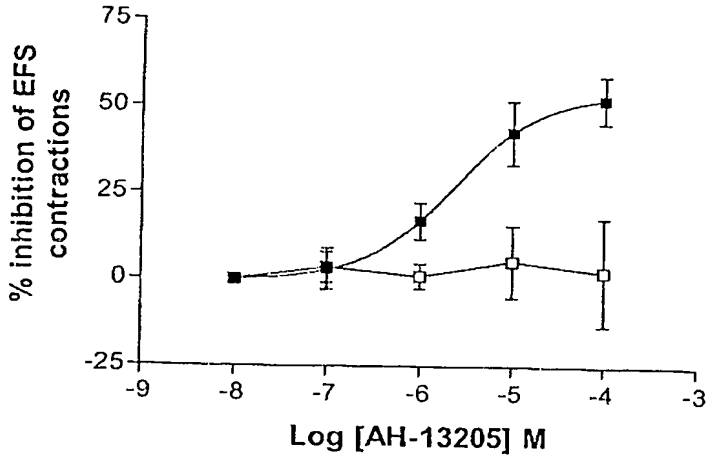

% inhibition of EFS contractions
75
50
25
0
-25
-9
-8
-7
-6
-5
-4
-3
Log [AH-13205] M

Fig. 7

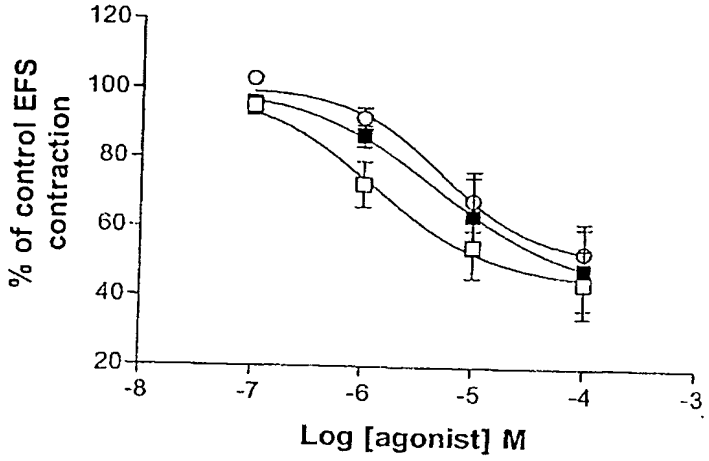

% of control EFS contraction
120
100
80
60
40
20
-8
-7
-6
-5
-4
-3
Log [agonist] M

Fig. 8

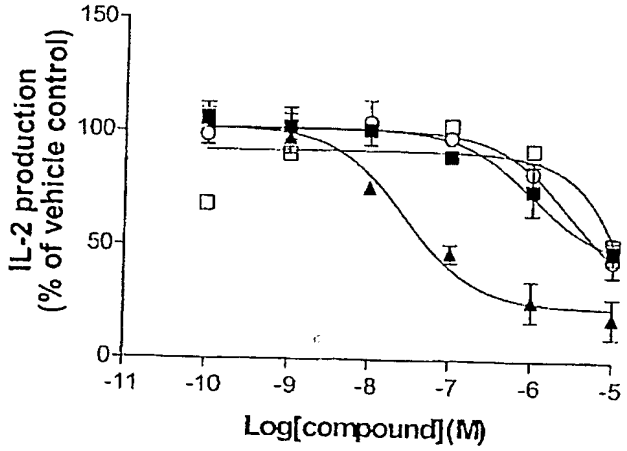

IL-2 production (% of vehicle control)
150
100
50
0
-11
-10
-9
-8
-7
-6
-5
Log[compound](M)

Fig. 9

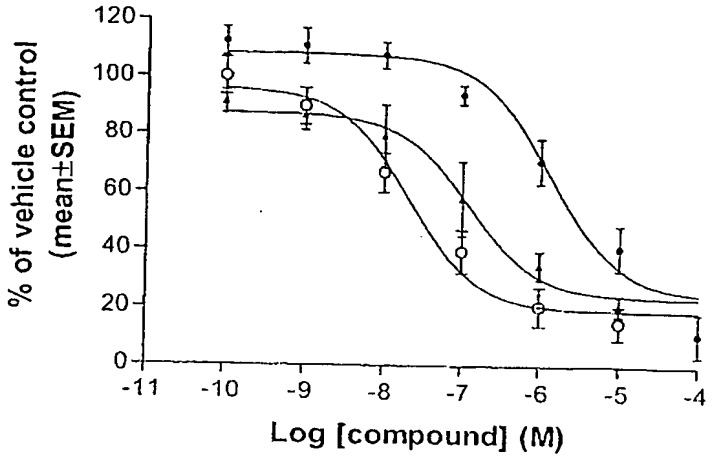

% of vehicle control (mean±SEM)
120
100
80
60
40
20
0
-11
-10
-9
-8
-7
-6
-5
-4
Log [compound] (M)

Fig. 10

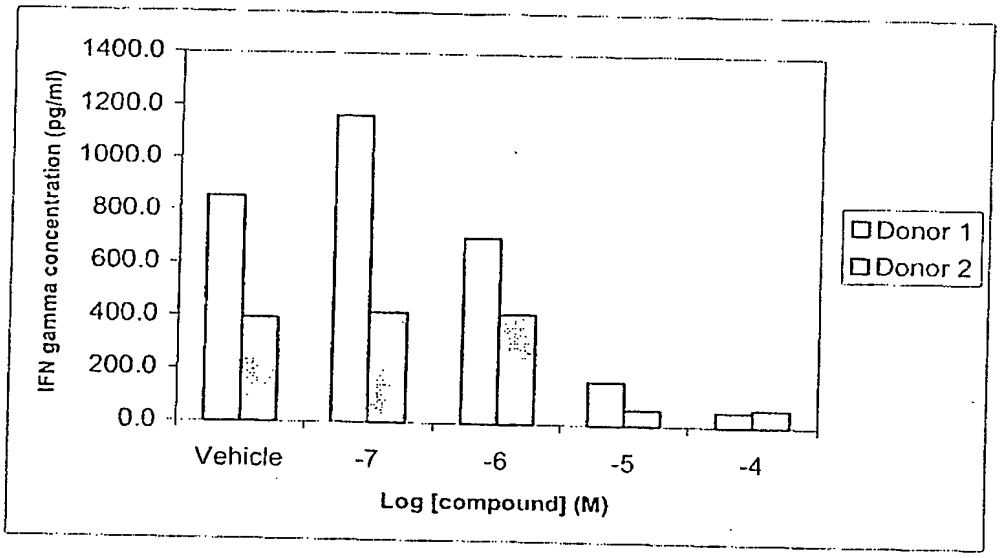

IFN gamma concentration (pg/ml)
1400.0
1200.0
1000.0
800.0
600.0
400.0
200.0
0.0
Vehicle
-7
-6
-5
-4
Log [compound] (M)
Donor 1
Donor 2

Fig. 11

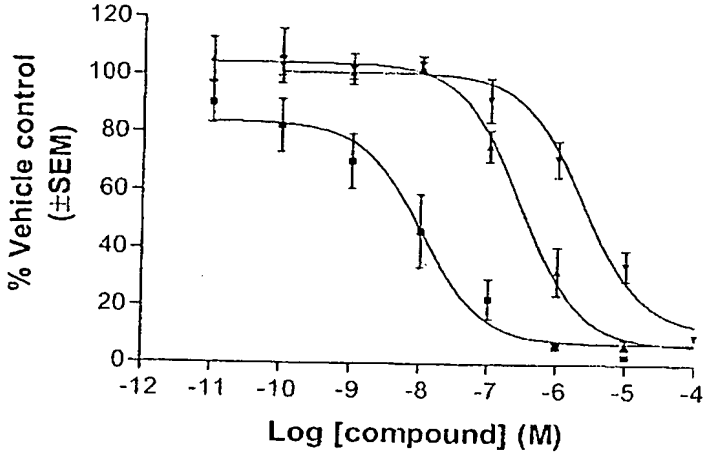

% Vehicle control
(±SEM)
120
100
80
60
40
20
0
-12
-11
-10
-9
-8
-7
-6
-5
-4
Log [compound] (M)

Fig. 12

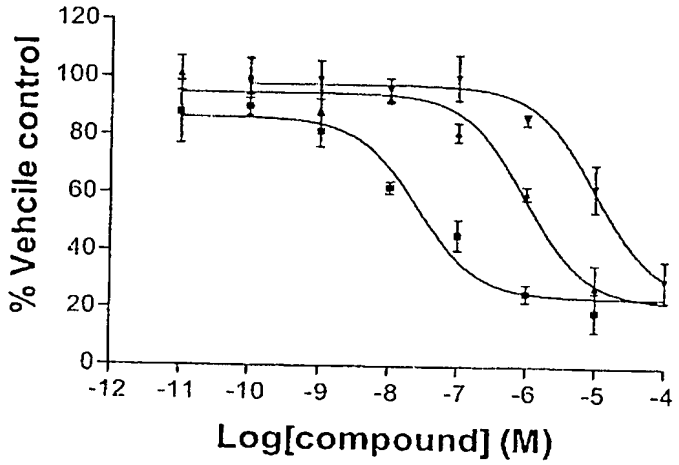

% Vehicle control
120
100
80
60
40
20
0
-12
-11
-10
-9
-8
-7
-6
-5
-4
Log[compound] (M)

Fig. 13

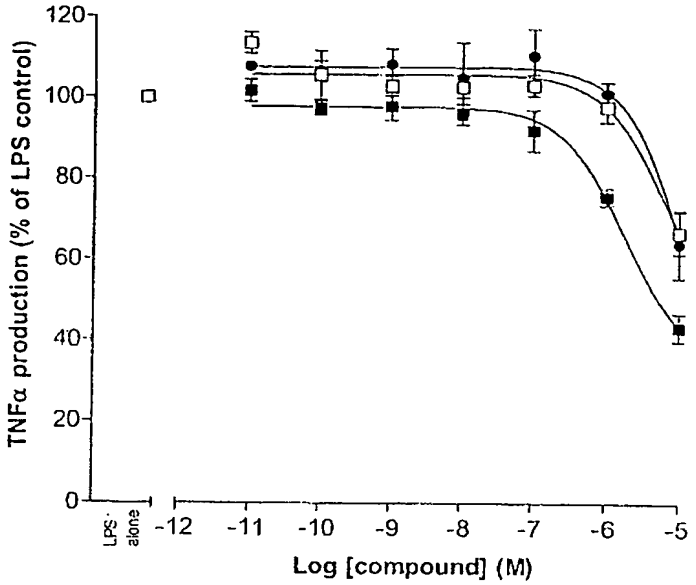

TNFα production (% of LPS control)
120
100
80
60
40
20
0
LPS alone
-12
-11
-10
-9
-8
-7
-6
-5
Log [compound] (M)

Fig. 14

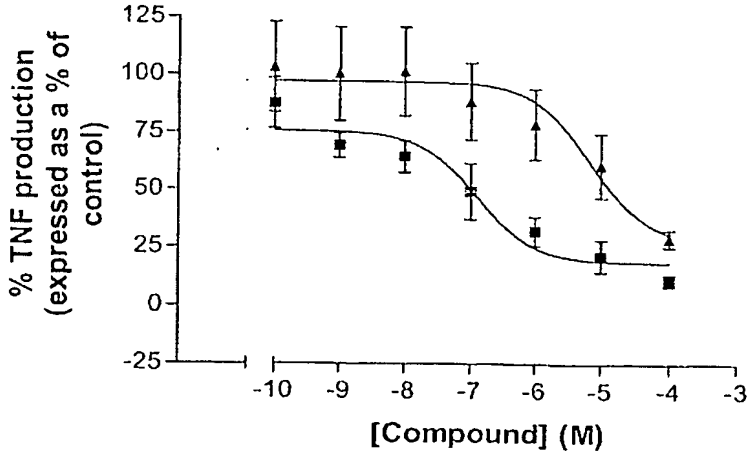

% TNF production (expressed as a % of control)
125
100
75
50
25
0
-25
-10
-9
-8
-7
-6
-5
-4
-3
[Compound] (M)

Fig. 15